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23 JUNE 1995 (23.06.95)

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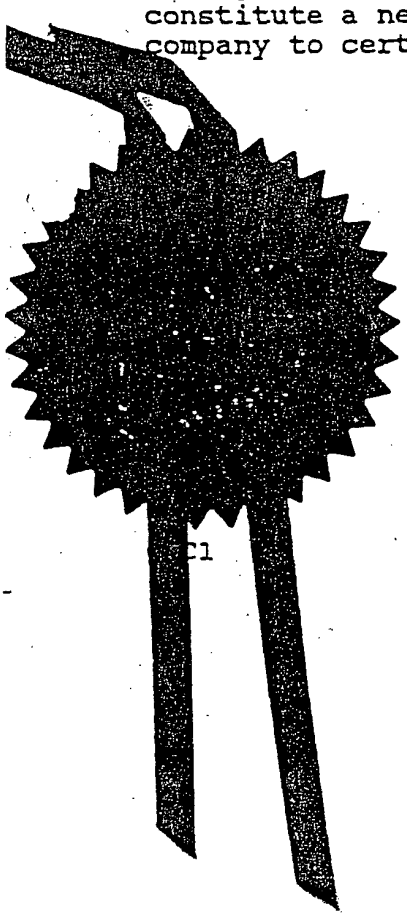

PRIORITY DOCUMENT

Signed M. Russell

Dated 16th May 1995

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12 MAY 1994

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9409496.8

Notes
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Rule 16 of the Patents Rules 1990 the main rule governing the completion and filing of this form.

The Patent Office — Request for grant of a Patent

Form 1/77

Patents Act 1977

❶ Title of invention

1 Please give the title of the invention: METHOD FOR IMPROVING GLYCAEMIC CONTROL IN DIABETES

❷ Do not give trading styles, for example, 'Trading as XYZ company', nationality or former names, for example, 'formerly (known as) ABC Ltd' as these are not required.

❷ Applicant's details

☐ **First or only applicant**

2a If you are applying as a corporate body please give:

Corporate name: LONDON HEALTH ASSOCIATION

Country *(and State of incorporation, if appropriate)*: Ontario, Canada

2b If you are applying as an individual or one of a partnership please give in full:

Surname

Forenames

2c **In all cases**, please give the following details:

Address: P.O. Box 5339
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ADP number *(if known)*: 566936100 2 AD /

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Yes [X] No [ ] ➡ *go to 3b*

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Agent's name	WITHERS & ROGERS
Agent's address	4 Dyer's Buildings Holborn London ENGLAND
Postcode	EC1N 2JT
Agent's ADP number	00001776001

3b: If you have appointed an agent, all correspondence concerning your application will be sent to the agent's United Kingdom address.

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Claiming an earlier application date

5 Are you claiming that this application be treated as having been filed on the date of filing of an earlier application?

Please mark correct box

Yes ☐ No ☒ ➡ *go to 6*

↓

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15(4) (Divisional) ☐ 8(3) ☐ 12(6) ☐ 37(4) ☐

Declaration of priority

If you are declaring priority from a PCT Application please enter 'PCT' as the country and enter the country code (for example, GB) as part of the application number.

Please give the date in all number format, for example, 31/05/90 for 31 May 1990.

6 If you are declaring priority from previous application(s), please give:

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❼ *The answer must be 'No' if:*
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there is an inventor who is not an applicant, or
● *any applicant is a corporate body.*

❼ Statement of Inventorship

7 Are you (the applicant or applicants) the sole inventor or the joint inventors?

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Yes [ ] No [X] ➡ ***A Statement of Inventorship on Patents Form 7/77 will need to be filed (see Rule 15).***

❽ *Please supply duplicates of claim(s), abstract, description and drawing(s).*

❽ Checklist

8a Please fill in the number of sheets for each of the following types of document contained in this application.

Continuation sheets for this Patents Form 1/77			N/A
Claim(s)	-	Description	06
Abstract	-	Drawing(s)	03

8b Which of the following documents also accompanies the application?

Please mark correct box(es)

Priority documents *(please state how many)*	
Translation(s) of Priority documents *(please state how many)*	
Patents Form 7/77 – Statement of Inventorship and Right to Grant *(please state how many)*	
Patents Form 9/77 – Preliminary Examination/Search	
Patents Form 10/77 – Request for Substantive Examination	

❾ *You or your appointed agent (see Rule 90 of the Patents Rules 1990) must sign this request.*

❾ Request

I/We request the grant of a patent on the basis of this application.

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METHOD FOR IMPROVING GLYCAEMIC CONTROL IN DIABETES

Glucagon-like peptide 1 or glucagon-like insulinotropic peptide (GLIP) is a gastrointestinal peptide which potentiates insulin release in response to glycaemia in normal humans. It has also been suggested as a useful adjunct to therapy with hypoglycaemic agents in type II or non-insulin dependent diabetes (Gutniak et al., (1992), N.E.J.M., Vol. 326, p. 1316). These authors have proposed that its role in type II diabetes might be to increase the subject's sensitivity to insulin.

The present inventors have found surprisingly, that administration of GLIP improves glycaemic control in insulin dependent type I diabetes (IDDM).

The recent findings of the Diabetes Control and Complications Trial (DCCT) carried out by the U.S. National Institute of Health have emphasised the importance of doing everything possible to normalise blood glucose levels in diabetics to avoid or delay micro-vascular damage. Intensified insulin therapy has been shown by the trial to improve glycaemic control but is accompanied by the risk of hypoglycaemia. This limits the degree of glycaemic control which can be safely attempted, so that true normalisation of blood glucose levels cannot be achieved with insulin therapy alone.

The present invention offers a method for improving glycaemic control in diabetes, while avoiding the risk of hypoglycaemia, by administration of an effective dose of GLIP.

SUMMARY OF DRAWINGS

Figure 1 shows blood levels of glucose (Panel A), C - peptide (Panel B), human pancreatic polypeptide (PP) (Panel C), glucagon (Panel D) and gastrin (Panel E) in Type I diabetic subjects after Sustacal meal alone (O) or Sustacal meal with GLIP infusion (•).

Figure 2 shows blood levels of glucose (Panel A) and C-peptide (Panel B) in Type I diabetic subjects during glucose infusion alone (○) or along with IV GLIP(●).

Figure 3 shows blood levels of glucose (Panel A) and C-peptide (Panel B) in Type I diabetic subjects after Sustacal meal and saline infusion (○) or Sustacal meal with infusion of 0.75 pm GLIP/kg/min (▲). Glucose and C-peptide values are expressed as the change (Δ) from baseline values at time zero.

Description of the Invention

The present invention provides a method for treating diabetes by improving glycaemic control in diabetics by administration of an effective dose of GLIP.

GLIP is used herein to mean GLIP-(7-36) amide or GLIP-(7-37), except where specifically relating to one of the examples, where GLIP-(7-36) amide was used.

As will be understood by those skilled in the art, the methods of the invention may be practised employing GLIP or an effective GLIP-related peptide, including an effective fragment of GLIP (7-37) or an effective analogue or derivative of GLIP (7-37).

In accordance with one embodiment of the invention, a method is provided for treating subjects suffering from insulin dependent diabetes (IDDM) by administration of an effective dose of GLIP.

In accordance with a further embodiment of the invention, a method is provided for treating diabetes by administration of an agent which reduces the rate of gastric emptying after meal ingestion.

In accordance with a further embodiment, a method is provided for reducing hunger and thereby reducing food intake in a human by administering an effective dose of GLIP to the human prior to food intake. The peptide is preferably administered shortly before food intake, in a dosage giving the required duration of action.

GLIP may be administered orally, nasally or parenterally. Parenteral administration may be by a variety of routes including subcutaneous or intravenous infusion, and subcutaneous or intravenous injection.

The subjects studied by the inventors were in the remission phase, or so-called "honeymoon phase", of IDDM characterised by substantial remaining endogenous insulin secretion.

As is seen in Figure 2, IV administration of GLIP along with intravenous glucose stimulated secretion of endogenous insulin in the subjects studied and gave improved control of blood glucose level.

The same dose of GLIP (1.2 pm/kg/min) gave excellent control of blood glucose level in these subjects after a meal, as seen in Figure 1, Panel A. Under these conditions, GLIP infusion also prevented a significant increase in blood levels of C-peptide.

After the Sustacal meal, the test subjects showed normal secretion of pancreatic polypeptide (PP) but this response was absent during GLIP infusion (Figure 1, Panel C). It is believed that this abrogation of PP response was due to the delayed passage of the meal from the stomach to the small intestine as a result of GLIP administration. That it was not due to a general suppression of gastrointestinal peptide secretion is indicated by the normal gastrin response to the presence of food in the stomach in these subjects (Figure 1, Panel E).

Administration of GLIP prevented the mean rise in plasma glucagon levels stimulated by the meal in the absence of GLIP. Gastrin levels were not significantly affected.

Administration of a lower dose of GLIP (0.75 pmol/kg/min) along with a meal resulted in some increase in blood glucose and C-peptide, as seen in Figure 3. Although the increase in glucose was less than in the

control experiment, the rise in C-peptide was similar to the control experiment.

When GLIP is used to improve glycaemic control in IDDM patients having residual endogenous insulin secretion capacity, both the insulinotropic effect of the hormone and its effect to delay gastric emptying will contribute to its effect. Some remission phase IDDM subjects may be sufficiently controlled by administration of GLIP alone, without exogenous insulin. The majority of subjects with true IDDM will likely require combination therapy with both insulin and GLIP.

Administration of GLIP can also improve glycaemic control in IDDM patients without endogenous insulin secretion, due to the delayed gastric emptying effect of the hormone. Other agents giving delayed gastric emptying may be similarly employed.

As indicated by these studies, the effect of GLIP on gastric emptying is dose related. The dose of GLIP to be administered may be optimised for each subject by evaluation of the degree of glycaemic control achieved by trial doses.

A convenient method of monitoring the rate of gastric emptying achieved in a subject by GLIP administration is the monitoring of blood levels of PP in response to various trial dose levels.

Another important finding by the present inventors is that subjects treated with GLIP after ingestion of a meal reported feelings of satiety and reduced appetite at the time the next meal would normally have been ingested. As diabetics frequently find the requirements for food intake and insulin administration at midday particularly irksome and an interference with work and other activities, this is an important finding with respect to diabetic management. By administering GLIP to diabetic subjects at breakfast time, along with administration of longer acting insulin if necessary, diabetics may be able

to omit lunch or greatly reduce the size of that meal, and thereby avoid the need for midday insulin.

By being able to control the rate of absorption of nutrients from the intestine in diabetics, in accordance with the methods of the invention, it should be possible to provide for better matching of the rate of absorption with the effect of endogenous or exogenous insulin.

An important advantage of improving glycaemic control by administration of a GLIP-related peptide is that there is little accompanying risk of inducing hypoglycaemia.

EXAMPLES

Example 1

7 subjects with remission phase Type I diabetes were studied after ingestion of a standardised meal of (delivering 30 kg/kg Sustacal (Upjohn). Subjects continued their normal insulin treatment programme on the day prior to the test and, on the day of the test, omitted their morning insulin injection and arrived fasting at 8:00 am. On one test day they were given the Sustacal meal, followed immediately by initiation of intravenous infusion of GLIP (synthetic human GLIP-(7-36)amide from Peninsula, U.K.) at an infusion rate of 1.2 pm/kg/min. Infusion was continued for 120 minutes. Blood levels of glucose, C-peptide, gastrin, glucagon and HPP were monitored by standard radioimmunoassay methods in samples taken before and at intervals during the study, up to 180 minutes. On another test day, subjects were given the Sustacal meal alone and the same analytes were similarly monitored.

Results are shown in Figure 1.

Example 2

Four subjects with remission phase Type I diabetes were studied during intravenous glucose infusion.

Subjects prepared for the tests as described in Example 1, but received an intravenous infusion of glucose (20 g over 60 min. constant rate) instead of the Sustacal meal. On one test day, they also received intravenous GLIP for 60 minutes (1.2 pm/kg/min for 60 min.) and on another test day, they received IV glucose alone. Blood levels of glucose and C-peptide were monitored as in Example 1.

The results are shown in Figure 2.

Example 3

Four subjects with remission phase Type I diabetes were studied during infusion with 0.75 pm/kg/min GLIP for 120 minutes after a Sustacal meal.

The test was conducted as described in Example 1 and blood glucose and C-peptide levels were measured. On a further test day, the subjects were studied during saline infusion after a similar Sustacal meal.

Results are shown in Figure 3.

(13)

Figure 1

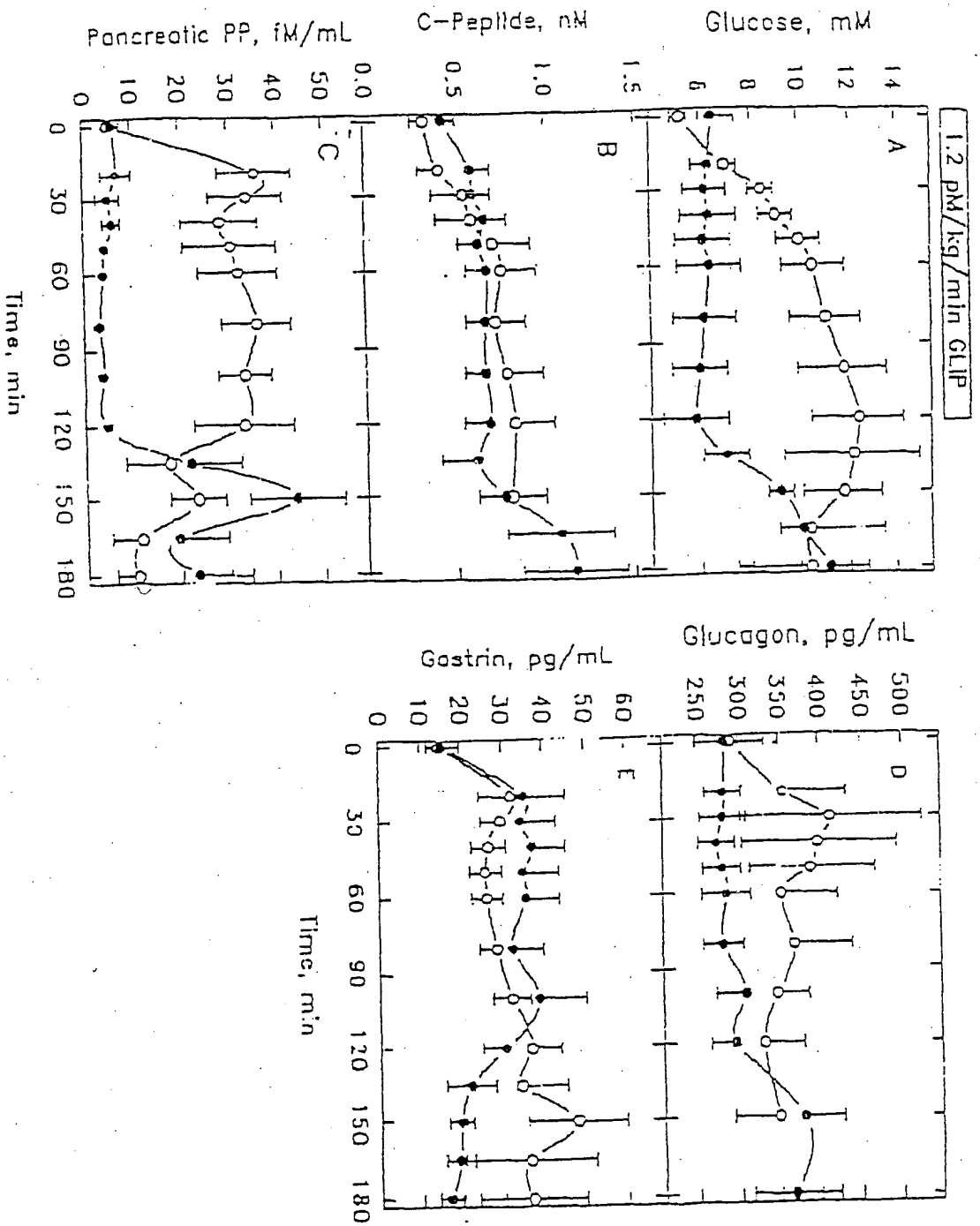
Glucose, mM
C-Peptide, nM
Pancreatic PP, fM/mL
1.2 pM/kg/min GLIP
A
B
C
Time, min
Glucagon, pg/mL
Gastrin, pg/mL
D
E
Time, min

Figure 2

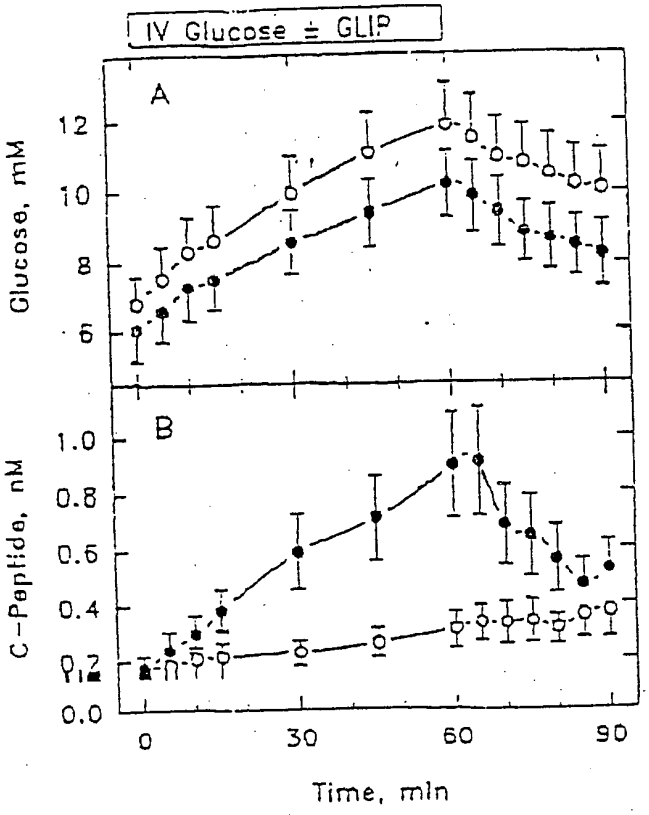

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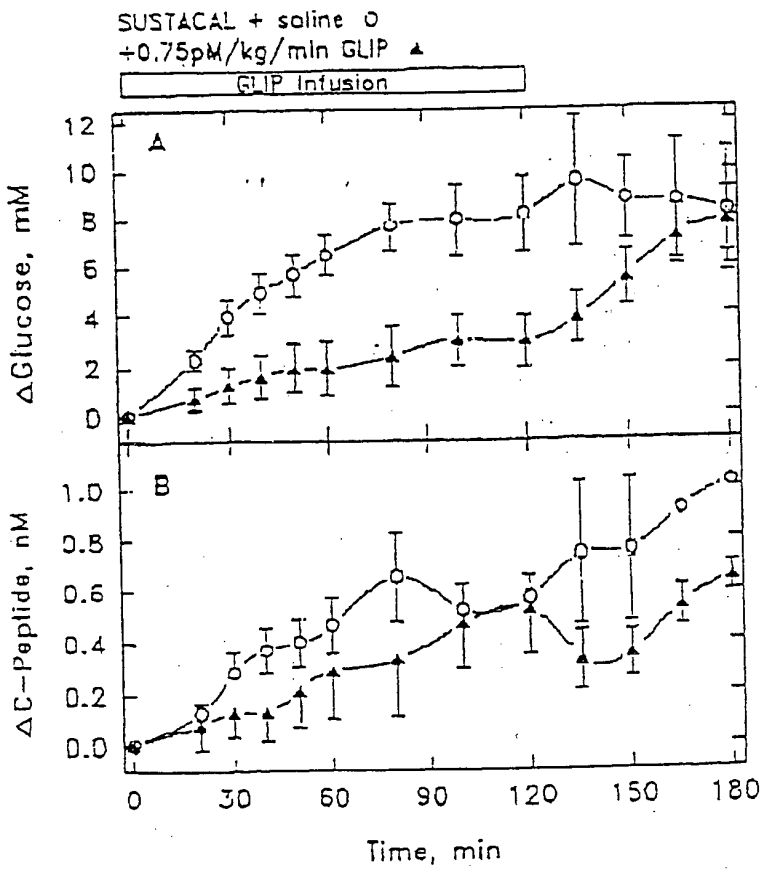
Figure 3



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